modifier group, selected from the group consisting of halo, sulfhydryl, azido, amino, monsubstituted amino and disubstituted amino groups [and] replacing a hydroxy group at the ribose sugar 2'-position.

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REMARKS

The claims of this invention concern methods for cleaving a target RNA molecule using ribozymes which contain modified nucleosides, with particular modifier groups at the ribose 2'-position. The modified ribozymes are more resistant to degradation than unmodified ribozymes.

Applicants have amended claim 44 to more particularly describe the claimed invention. Support for the amendment can be found, for example, by the descriptions provided in the present application on page 5, third full paragraph, and page 10, third paragraph. These amendments are made without prejudice, and do not constitute amendments to overcome any prior art rejections under 35 U.S.C. §103. The amendment does not constitute an admission that prior claim 44 is unpatentable and should not be so construed. Applicant reserves the right to prosecute such claims in the future.

Double Patenting Rejection

Claims 44-46, 48, 50-57 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 5,672,695 (U.S. Serial No. 07/965,411).

Applicants provide herewith a Terminal Disclaimer to overcome the double-patenting rejection.

Rejection under 35 USC § 112

The Examiner rejected claims 44-57 under 35 U.S.C. § 112, paragraph 1, alleging that the claimed invention is drawn to modifications comprising any modifier group replacing the 2' hydroxy of the ribose sugar whereas "the specification as filed teaches only ribozymes with modified nucleotides having 2'-halo and 2'-amino cleaving RNA." This rejection is respectfully traversed.

Applicants submit that newly amended claim 44 obviates the Examiner's rejection concerning the breadth of the claims encompassing any modifier groups. This amendment is made without prejudice, and does not constitute amendment to overcome any prior art rejections under 35 U.S.C. §103. The amendment does not constitute an admission that prior claim 44 is unpatentable and should not be so construed. Applicant reserves the right to prosecute such claims in the future.

The Examiner also asserts that that no guidance is provided to identify at what positions such modifiers can be tolerated in ribozyme motifs.

Applicants submit that they have shown in Example 4 how those skilled in the art can test modified ribozymes to determine if a particular modification affects the catalytic activity of a ribozyme (see, pages 24-27 of the specification). In Example 4, Applicants show that by determining kcat/km values a person skilled in the art can quantitate the effects 2'-hydroxy modifications have on the catalytic activity of a ribozyme. Therefore, one skilled in the art, at the time the application was filed, could test any of the claimed modified ribozymes against a potential target using the approach disclosed by the Applicants in Example 4.

The Examiner also alleges that the specification as filed fails to provide any general or particular guidance to resolve the unpredictable factors concerning the engineering and delivery of ribozymes to cleave target in cells and that "de novo experimentation" would have to be engaged to practice the invention as broadly claimed. In particular, the Examiner relies on an article by Branch as evidence of the unpredictability of engineering and delivering ribozymes.

Applicants submit that one skilled in the art could practice the claimed invention without having to engage in undue experimentation.

With respect to the Examiner's assertion concerning unpredictability of ribozyme delivery, Applicants' specification identifies two general methods for delivery of ribozymes into target cells: 1) exogenous delivery, which involves insertion of preformed ribozymes into target cells; and 2) endogenous delivery, which involves transcription of a ribozyme-encoding artificial gene in a cell (see, specification page 3). At the time of filing the present specification, methods for delivering ribozymes into cells using endogenous delivery were well known in the art and are demonstrative of delivery of nucleic acids into cells. For example, Cameron and Jennings (1989, *PNAS USA*, 86:9139-43) used plasmids containing DNA encoding ribozymes to demonstrate *in*

vivo delivery and activity of ribozymes in monkey cells. Sarver et al. (1990, *Science*, 247:12222-1225) used a mammalian expression vector expressing ribozymes to show that ribozymes against HIV-1 *gag* RNA were effective in reducing p24 expression in HeLa cells.

The data generated, for example, by Cameron and Jennings, and Sarver et al. provides evidence that those skilled in the art could reasonably expect success in delivering nucleic acid molecules (e.g., ribozymes) for *in vivo* use. The successful transfection of eukaryotic cells using techniques applicable to transfecting plasmids would be expected to have a high probability of success to those skilled in the art, especially since preformed ribozymes are much smaller than the plasmids used by Cameron and Jennings and Sarver et al. In addition, the claimed ribozymes are stabilized against degradation, which would thereby substantially increase the lifetime of the ribozyme.

Applicants also submit the attached Declaration of Dan T. Stinchcomb, Ph.D., which further demonstrates that the claimed methods can be practiced for *in vivo* use without involving undue experimentation. The Stinchcomb declaration was submitted in connection with the prosecution of a related U.S. patent application (U.S. Serial No. 08/434,547, now U.S. Patent No. 5,817,635), which was a divisional of the parent of the present application (Appl. Serial No. 07/965,411, now U.S. Patent 5,672,695). The Declaration is applicable to the present case as well. As explained in the Stinchcomb declaration, modified ribozymes can readily be delivered to cells using a variety of approaches known in the art. Of note is the fact that many of the examples cited in the Stinchcomb declaration, which demonstrate *in vivo* delivery of ribozymes, employ techniques that were available to those skilled in the art at time the present application was filed. For example, at paragraph 11, the Stinchcomb declaration describes the delivery of ribozymes targeted against HIV into CD4+ cells as complexes with calcium phosphate. Transfection of nucleotides into eukaryotic cells using calcium phosphate was well known in the art before the filing of the present application (see, e.g., Sambrook, et al., Molecular Cloning, A Laboratory Manual, 2nd. Ed., 1989, section 16.32.).

Stinchcomb also describes the exogenous delivery of ribozymes into eukaryotic cells using cationic lipids (see, paragraphs 9 & 10). Cationic lipids were also well known in the art prior to filing of the present application (see, Malone et al., 1989, *PNAS USA*, 86:6077-6081). Therefore, the Stinchcomb declaration demonstrates the successful *in vivo* delivery of ribozymes

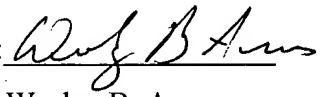
using techniques (calcium phosphate, and cationic lipids) which were well known in the art at the time the present application was filed. Because these techniques were well known in the art at the time of filing the present application, a person skilled in the art was enabled to practice the claimed invention without undue experimentation.

Accordingly, as shown by the preceding discussion, the pending claims are in condition for allowance and a notice to that effect is respectfully requested.

Enclosed is a check in the amount of $490.00 for the fee (Small Entity) required under 37 C.F.R. §1.136 for the timely filing of a response up to and including May 27, 1999, and the fee ($55.00) for the terminal disclaimer filed with this response.

If the above amount is incorrect or if any additional fees are due in connection with this response, please charge or credit Deposit Account No. 12-2475 for the appropriate amount.

Respectfully submitted,
LYON & LYON LLP

By: 
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